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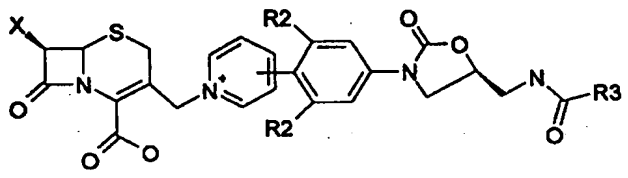

(I)

(57) Abstract

The present invention relates to novel cephem derivatives in which known phenyl oxazolidinone derivatives are chemically combined with cephem, a process for producing the cephem derivatives, and a pharmaceutical antibacterial composition containing the cephem derivatives. The structural formula of the cephem derivatives compounds is represented as in formula (I).

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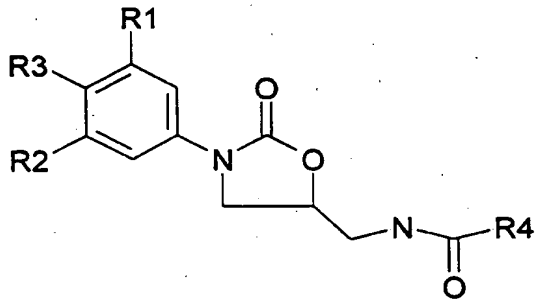
CEPHEM DERIVATIVES AND A METHOD FOR PRODUCING THE COMPOUNDS AND AN ANTIBACTERIAL COMPOSITION CONTAINING THE COMPOUNDS

FIELD OF THE INVENTION

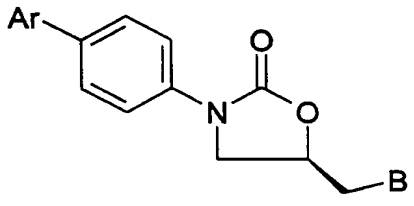
The present invention relates to novel cephem derivatives in which known phenyl oxazolidinone derivatives are chemically combined with cephem, a process for producing the cephem derivatives, and a pharmaceutical antibacterial composition containing the cephem derivatives.

BACKGROUND OF THE INVENTION

International Patent Publication No. WO 93/09103 discloses substituted aryl- and heteroaryl-phenyl oxazolidinones which may be useful as antibacterial agents. The structural formula is represented as follows:



US Patent No. 5,254,577 discloses aminomethyloxooxazolidinyl arylbenzen derivatives which can be used as antibacterial agents. The structural formula is represented as follows:

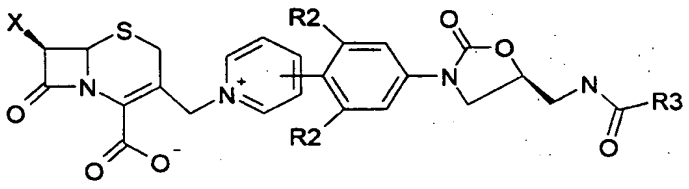


Some of pyridine-substituted phenyl oxazolidinone derivatives disclosed in the above patents are effective against Gram-positive bacteria such as *Staphylococcus aureus* and *Streptococcus pneumoniae*. However, they are not active against Gram-negative bacteria such as *Escherichia coli*, *Klebsiella*, *Proteus*, and *Seratia marcenses*. Moreover, they cannot be administered as an injection solution because their free amine forms are little soluble.

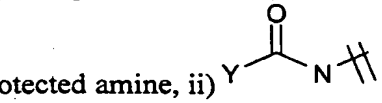
The inventors have intensively studied to develop new antibacterial agents which have effective and excellent activity against Gram-negative bacteria and Gram-positive bacteria, and which are soluble so that they can be used as an injection solution. As a result, the structurally new compounds were produced by chemically reacting known antibacterial oxazolidinone compounds with cephem compounds. They were found to be potently active against Gram-negative bacteria as well as Gram-positive bacteria.

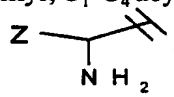
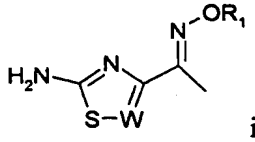
SUMMARY OF THE INVENTION

The present invention provides compounds of the formula I:



or pharmaceutically acceptable salts or hydrates thereof wherein

X is i) amine or protected amine, ii)  in which Y is i) hydrogen, ii) C_1-C_6 lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4 acyloxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl,

and carboxylic acid and inorganic cation salt thereof, iii) C_2-C_6 alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4 acyloxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C_2-C_6 alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4 acyloxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, vi) R4-(CH_2)n-, in which n is an integer of 0 to 3, and R4 is 2-thiophenyl, 2-furyl, 2-pyrolyl, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 acylamino, C_1-C_4 alkylsulfonylamino, C_1-C_4 alkoxy, and C_1-C_4 acyloxy, vii)  in which Z is hydrogen, or C_1-C_6 lower alkyl, C_1-C_6 alkenyl, C_2-C_6 alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4 acyloxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, and carbon having optical activity can be optically pure (-), (+) or racemic forms, viii)  in which W is CH or N, R_1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or

inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different;

R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and

provided that in the compounds of the formula I the phenyloxazolidinone is substituted at 3 or 4 positions of pyridine.

DETAILED DESCRIPTION OF THE INVENTION

"Lower alkyl" herein means, unless indicated otherwise, straight or branched alkyl having from 1 to 6 carbons and cycloalkyl having from 3 to 6 carbons. For example, C_1-C_6 alkyl include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and structural isomers thereof.

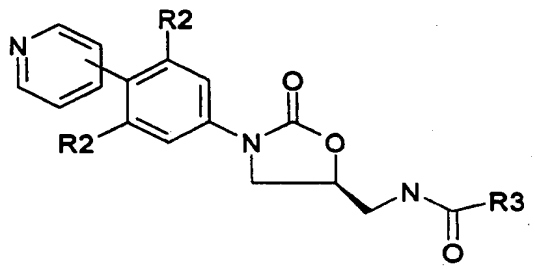
The R3 substituents are preferably hydrogen, methyl, difluoromethyl, dichloromethyl, hydroxymethyl, or methoxy and, most preferably, methyl.

The most preferred absolute configuration at C-5 of the oxazolidinone ring of the compounds according to the present invention is (S) under the Cahn-Ingold-Prelog nomenclature system. It is the (S)-enantiomer which possesses excellent activities against bacteria. The racemic mixture can be used in the same way and for the same purpose as the pure (S)-enantiomer. However, the difference is that twice as much reacemic material must be used to exhibit the same antibacterial activity as the pure (S)-enantiomer.

The pharmaceutically acceptable salts of the compounds I include inorganic cation salts such as alkaline metal salts (e.g., sodium or potassium) and alkaline earth metal salts (e.g., calcium or magnesium), inorganic salts such as hydrochloride,

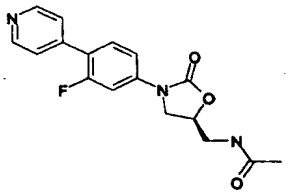
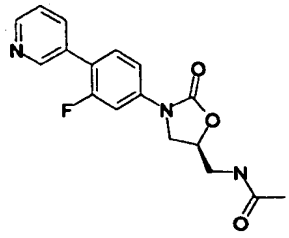
hydrobromide, hydroiodide and sulfate, organic salts such as malate, lactate and tartarate, organic sulfonate such as benzenesulfonate, methanesulfonate and 4-tolunesulfonate, amino acid salts such as arginine, lysine and glycine, and amine salts such as trimethylamine, ammonia, triethylamine, pyridine, and picoline.

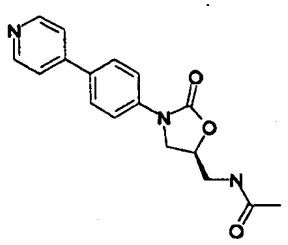
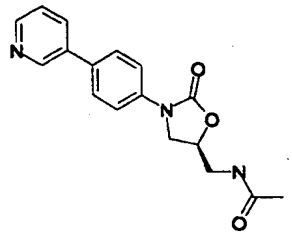
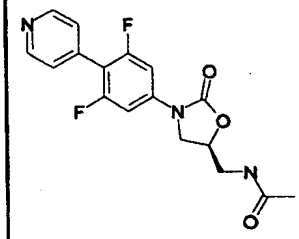
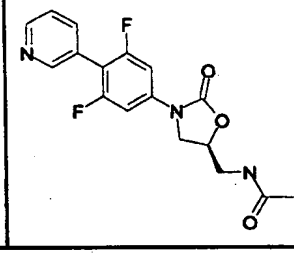
Examples of the substituents at C-3 position of cephem include the compounds of the formula II:



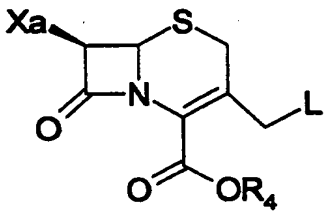
The specific examples of the compounds of the formula II are indicated in Table 1 below.

Table 1

NO.	Structural Formula	Compound Name	Reference for Synthesis
1		(S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	WO 93/09103
2		(S)-N-[[3-[3-3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	WO 93/09103

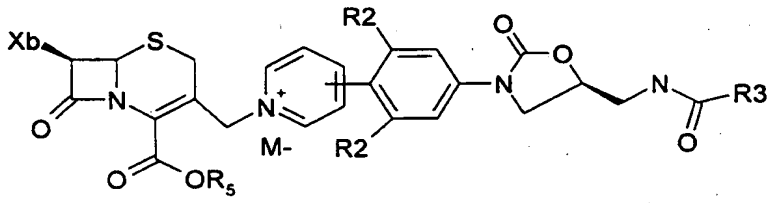
3		(S)-N-[[3-[4-(4-pyridyl) phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	USP 5254577
4		(S)-N-[[3-[4-(3-pyridyl) phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	USP 5254577
5		(S)-N-[[3-[3,5-difluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	WO 93/09103
6		(S)-N-[[3-[3,5-difluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl] acetamide	WO 93/09103

The compounds I or pharmaceutically acceptable salts thereof of the present invention can be produced by reacting the above compounds II with the compounds of the formula III:

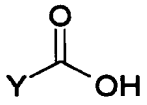


wherein Xa is the same as X defined above, except for amine and protected amine, R_4 is hydrogen or carboxylic acid-protecting group, and L is halogen atom or acetoxy. The halogen atom is chlorine, bromine or iodine. Bromine or idodine is especially preferable.

Alternatevely, the compounds I of the present invention can be produced by acylating the compounds of the formula V:

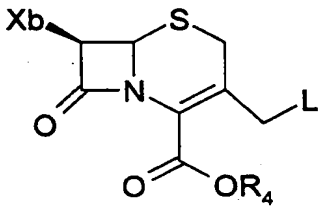


wherein Xb is amine or protected amine, R_5 is hydrogen or carboxylic acid-protecting group, M^- is anionic halogen such as chloride, bromide or iodide, or sulfonate, acetate, benzenesulfonate or citrate anions, with the compounds of the formula VI:



wherein Y is the same as defined above. The most preferred anion M^- is chloride or bromide. In the absence of M^-, the inner salt formed by monovalent anion of carboxylate and monovalent cation of pyridine is also preferable.

The compounds V can be prepared by C-3 reacting the compounds II with the compounds of the formula IV:



wherein Xb is amine or protected amine, R_4 is hydrogen or carboxylic acid-protecting group, and L is the same as defined above.

The reaction of the compounds II and the compounds III can be carried out at the temperature of from -30°C to 70°C. The preferred solvent is anhydrous solvent. The suitable organic solvents include lower nitrile such as acetonitrile and propionitrile, halogenated alkane such as chloroform, tetrachloromethane and dichloromethane, ether such as tetrahydrofuran and dioxane, amide such as N,N-dimethylformamide and N,N-dimethylacetamide, ester such as ethylacetate and methylacetate, ketone such as acetone, methylethylketone and methylisobutylketone, sulfoxide such as dimethylsulfoxide, aromatic hydrocarbon such as bezene and toluene, and mixtures thereof.

Protecting groups which do not participate in the displacement reaction of the compounds II and III may be introduced to amine, carboxyl and alcohol groups of the compounds II and III. Examples of the amine-protecting group include formyl, acetyl, chloroacetyl, dichloroacetyl, t-butoxycarbonyl, benzyloxycarbonyl, triphenyl, benzyl, 4-methoxybenzyl, diphenylmethyl, triloweralkylsilyl and trimethylsilyl. The carboxyl-protecting groups include for example t-butyl, benzyl, 4-methoxybenzyl, benzyl, 4-nitrobenzyl, diphenylmethyl, methyl, 2,2,2-trichloroethyl, pivaloyloxymethyl, triloweralkylsilyl and trimethylsilyl. Examples of the alcohol-protecting group include acetoxy, methoxymethyl, tetrahydrofuranyl, t-butyl, benzyl, and 4-methoxybenzyl.

Alternatively, amine, carboxyl and alcohol groups of the compounds II and III can be simultaneously protected by silylation. N,O-bis(trimethylsilyl)acetamide, N-methyl-N-(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-(trimethylsilyl)trifluoroacetamide and the like can be used as a silylating reagent. The silylating reagents are advantageous in that they make it possible to simultaneously protect amine, carboxyl and alcohol groups in an anhydrous solvent such as dichloromethane.

When L in the compounds IV is halogen atom such as bromine or iodine, the

compounds V can be obtained by reacting the compounds II with a silylating reagent such as N,O-bis(tri-loweralkylsilyl)acetamide or N,O-bis(tri-loweralkylsilyl) trifluoroacetamide in an anhydrous solvent such as dichloromethane or acetone at the temperature of from -30° to 60°C, followed by, if necessary, deprotecting, and crystalizing into hydrochloride, hydroiodide or sulfate salts or chromatographing over silical gel, alumina, resin, and the like.

When L in the compounds IV is acetoxy, e.g., the compound IV is 7-amino-3-acetoxymethyl-3-cephem-4-carboxylic acid (7-ACA), the compounds V can be obtained by simultaneously protecting amine and carboxyl groups with a silylating reagent such as N,O-bis(tri-loweralkylsilyl)acetamide, N,O-bis(tri-loweralkylsilyl)trifluoroacetamide or
hexamethylsilazane(HMDS) and then converting acetoxymethyl into iodomethyl using iodotrimethylsilane.

The protection and deprotection of the functional groups can be conducted by a conventional method in the art, for example, "Protective groups in Organic Synthesis, 2nd edition" (Greene, T.W., etc., John Wiley & Sons, New York, 1991). The pharmaceutically acceptable salts of the compounds II and III are the same as mentioned in the compounds I.

The compounds II as the substituents at C-3 position of cephem, for example, (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide, are known and can be synthesized by methods described in International Patent Publication No. WO 93/09103 and US Patent No. 5254577.

The compounds I of the present invention can be isolated and purified by conventional extraction, crystallization and column chromatography in the art.

The antibacterial composition containing the compounds I or pharmaceutically acceptable salts thereof as an active ingredient can be formulated into solid or liquid

using conventional techniques in the art. The pharmaceutical composition of the present invention can be primarily adminstered by intravenous or intramuscular injections. In addition, the composition of the present invention can be used in the forms of capsule, tablet, powder, suppository, and the like.

Examples of the solid form containing the compounds I include powder, tablet, capsule, suppository, cachet, and the like. The solid form can contain at least one of thickener, flavourant, sweetener, solubilizer, lubricant, suspending agent, binder, encapsulating agent, and the like. Examples of nonactive solid carrier include magnesium carbonate, magnesium stearate, talc, glucose, lactose, pectin, dextrin, starch, gelatin, wax, coccoa butter, and the like. The liquid formulation can be solution, suspension or emulsion. Examples of the carrier for the liquid form include water, mixture of water and propyleneglycol, mixture of water and polypropyleneglycol, and the like. Additionally, additives such as pigment, solubilizer, sweetener, stabilizer, thickener, and the like can be included in the liquid formulation.

The antibacterial composition of the present invention can be applied directly to human and animals. In addition, it can be used as food preservatives, agricultural chemicals, and the like. When the composition of the present invention is used in the treatment of human or animals against microbial infection, the injection or oral administration is preferable.

The adminstration amount of the compounds I depends on sexuality, age, weight and symptom of the patients to be treated, administration route, and the like. Generally, the daily dosage is in the range of 1 mg/kg and 1,000 mg/kg. The preferable daily dosage is between 100 mg/kg and 500 mg/kg.

The compounds I of the present invention have broad activity against Gram-positive bacteria such as *Streptococcus*, *Staphylococcus*, *Conellebacterium*, *Baccilus*, *Enterococci*, and the like, and Gram-negative bacteria such as *Escherichia coli*, *Klebsiella*, *Serratia marcescens*, *Salmonella*, *Proteus*, and the like. Particularly, the

compounds I are effective against strains which are resistant to known antibiotics such as vancomycin, β-lactam antibiotics, quinolones, and the like.

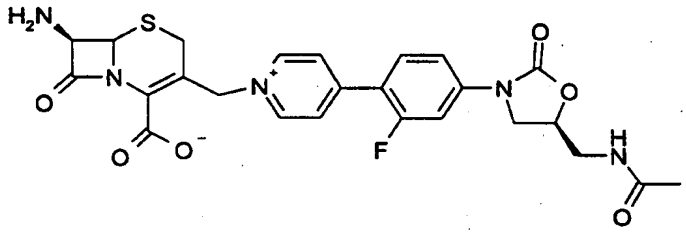
The compounds I of the present invention are greatly valuable in that they can be used as an injection because their water solubility is at least 10%. In comparison, the known compounds indicated in the above Table 1 are active in vitro against Gram-positive bacteria and drug-resistant strains but their free bases cannot be used as an injection because of low solubility.

The invention will now be described with reference to the following illustrative Examples.

EXAMPLES

Reference Example 1

Preparation of 7β-amino-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



3.8 ml of hexamethyldisilazane was added to a suspension of 4.15 g of 7-aminocephalosporinic acid (7-ACA) in 50 ml of dichloromethane. 1 or 2 drops of iodotrimethylsilane were then added and the solution was refluxed with heat under nitrogen for 2 hours. 1.95 ml of chloromethylsilane was added and the solution was refluxed with heat for 30 minutes. The reaction mixture was cooled to 25°C. 8.35 ml of dimethylaniline was added and the solution was stirred for 30 minutes. 2.84 ml of iodotrimethylsilane was added under nitrogen and the solution was stirred at 20°C for 1.5 hours.

The resulting solution was mixed with the silylated pyridine derivative at 5°C, and the solution was stirred at 20°C for 2 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the method described in international patent publication No. WO 93/09103. 5.65 g of the prydine derivative was mixed with 30 ml of acetonitrile. The resulting solution was reacted with 9.57 ml of N,O-bis(trimethylsilyl)acetamide at 25°C for 2 hours to produce the silylated pyridine derivative. After the reaction was completed, a mixed solvent of 2.0 ml of methanol, 145 ml of acetone and 2.2 ml of water was slowly dropwise added so that deprotection took place. The reaction mixture was stirred at 5°C for 1 hour and the resulting solid was filtered under reduced pressure. The solid was washed with 3 x 20 ml of acetone and 2 x 30 ml of diethylether, and was dried under vaccum at 35°C to obtain 9.2 g of the title compound as hydroiodide salt. 5.0 g of the hydroiodide salt was mixed with 25 ml of water and 25 ml of acetone. The resuting solution was cooled to 10°C, and then 2 ml of concentrated hydrochloric acid was added to the solution and the reaction mixture was stirred for 30 minutes. 1 g of activated carbon was added to the solution, and the solution was then stirred for 30 minutes, and filtered. The filtrated was warmed to 25°C, and 25 ml of anhydrous ethanol and 100 ml of isopropylalcohol were slowly added to the solution. The reaction mixture was cooled to 5°C to yield precipitating crystals. 100 ml of isopropylalcohol was added to the solution and the resulting solution was stirred for 30 minutes. The solution was filtered under reduced pressure, washed with 3 x 20 ml of isopropylalcohol, 2 x 20 ml of acetone and 2 x 30 ml of diethylether, and dried under vacuum at 35°C to obtain 2.5 g of dihydrochloride salt of the title compound.

mp: 140°C to 169°C (decomposition).

NMR(400MHz, DMSO-d6):

9.08~9.11(2H,d,J=7.1 Hz), 8.43~8.46(2H,d,J=6.3 Hz), 8.32(1H,t), 7.96~8.02(1H,dd), 7.73~7.79(1H,dd), 7.60~7.63(1H,dd), 5.58~5.67(1H,dd), 5.17~5.23(3H,m), 4.82(1H,m), 4.20~4.24(1H,t), 3.84~3.88(1H,dd), 3.54~3.68(2H,ABq,J=18.2Hz), 3.44~3.47(2H,m), 1.84(3H,s)

Reference Example 2

Preparation of 2-(4-methoxybenzyloxy)acetic acid

1 g of ethylglycolate was dissolved in 10 ml of dimethylformamide. The solution was cooled to 5°C. 0.38 g of 60% sodium hydride was added to the solution. The solution was stirred for 10 minutes and was reacted with 1.3 ml of 4-methoxybenzylchloride at 25°C for 2 hours. The solution was extracted with 10 ml of water and 20 ml of ethylacetate. The aqueous layer was extracted with 10 ml of ethylacetate, and the collected orgaic layer was washed with 2 x 20 ml of water and 10 ml of brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The resulting oily residue was dissolved in 10 ml of anhydrous ethanol. The resulting solution was mixed with an aqueous solution of 0.4 g of sodium hydroxide in 0.2 ml of distilled water and the mixture was stirred for 3 hours. 10 ml of ethylacetate and 10 ml of water were added to the solution, and the solution was then stirred for 30 minutes. After the layers were separated, the organic layer was removed. 2N HCl was added to the aqueous layer to adjust its pH to 1.0. The solution was extracted with 2 x 10 ml of dichloromethane, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to obtain 1.3 g of the title compound.

mp: 52°C to 53°C

NMR(400MHz,DMSO-d6):

8.07(1H,s), 7.25(2H,m), 6.86(2H,m), 4.54(2H,s), 4.08(2H,s), 3.79(3H,s)

Reference Example 3

Preparation of 2-(4-methoxybenzyloxy)propanoic aicd

Following the above Reference Example 2, but using ethyl(S)-(-)-lactate as a starting material, the title compound was prepared.

mp: 53°C to 54°C

NMR(400MHz,CDCl3):

7.29(2H,d), 6.89(2H,d), 4.62~4.48(2H,dd), 4.08(1H,q), 3.80(3H,s), 1.47(3H,d)

Reference Example 4

Preparation of 1H-1-imidazole acetic acid hydrochloride

5 g of immidazole was added to 50 ml of tetrahydrofuran and the resulting solution was cooled to -30°C. The cold solution was mixed with 3.2 g of 60% sodium hydride and the solution was stirred for 10 minutes. The solution was then reacted with 10.8 ml of tert-butylbromoacetate at the same temperature for 1 hour. The solution was slowly warmed to 25°C and was stirred for 1 hour. The reaction mixture was extracted with 30 ml of water and 100 ml of ethyl acetate. The organic layer was dried over anhydrous sodium sulfate, filtered under reduced pressure, and concentrated under reduced pressure. Oily unpurified substances were mixed with 50 ml of ethyl ether and the mixture was stirred for 30 minutes. The resulting solid was isolated and dried to obtain 12.9 g of tert-butyl-1H-1-imidazole acetate. 2 g of tert-butyl-1H-1-imidazole acetate was dissolved in 20 ml of tetrahydrofuran and the resulting solution was reacted with 0.5 ml of 6N HCl at 55°C for 3 hours. The reaction mixture was concentrated under reduced pressure. The residue was added to 10 ml of ethylether, and the resulting solid was filtered and dried to obtain 1.0 g of the title compound.

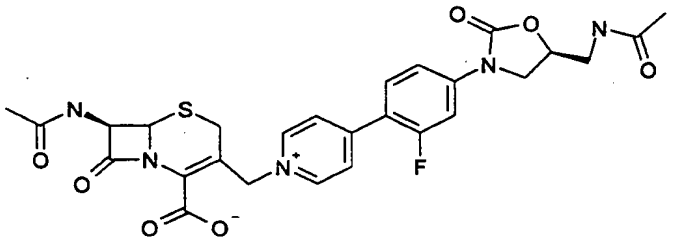
mp: 208°C to 210°C

NMR(400MHz,DMSO-d6):

9.41(1H,s), 7.92(1H,s), 7.67(1H,s), 5.17(2H,s)

Example 1

Preparation of 7β-acetamido-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



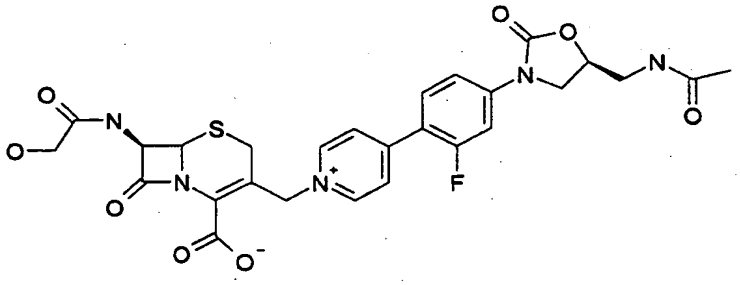
1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 20 ml of dichloromethane and 3 ml of methanol, and the resulting solution was cooled to 5°C. The cold solution was mixed with 0.74 ml of triethylamine, and the solution was stirred for 10 minutes. 0.7 ml of acetic anhydride was dropwise added to the solution for 10 minutes, and the solution was then stirred for 30 minutes. After the reaction was completed, the solvent was removed under reduced pressure. The residue was dissolved in an aqueous 50% ethanol, and the solution was concentrated under reduced pressure. The residue was chromatographed on silica gel using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure, and lyophilized to obtain 50 mg of the title compound.

NMR(400MHz, DMSO-d6):

9.49~9.52(2H,d), 8.75~8.78(1H,d), 8.37~8.40(2H,d), 8.27(1H,t), 7.93~7.98(1H,t), 7.73~7.78(1H,dd), 7.59~7.62(1H,dd), 5.54~5.59(1H,dd,J=3.8Hz),5.03~5.70(2H,ABq,J=13.4Hz), 5.02~5.04(1H,d), 4.82(1H,m), 4.20~4.25(1H,t), 3.84~3.88(1H,dd), 3.08~3.58(2H,ABq,J=17.5Hz), 3.45~3.48(2H,m), 1.85(3H,s), 1.84(3H,s)

Example 2

Preparation of 7β-[2-hydroxy-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 20 ml of dichloromethane and 3 ml of methanol and the resulting soltion was cooled to 5°C. The cold solution was mixed with 0.74 ml of triethylamine

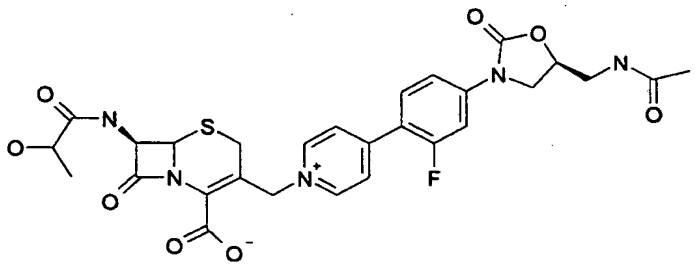
and the solution was then stirred for 10 minutes. 1 g of 2-(4-methoxybenzyloxy)acetic acid in the Reference Example 2 was dissolved in 10 ml of dichloromethane and the resulting solution was cooled to -30°C. The solution was reacted with 0.72 ml of triethylamine and 0.62 ml of pivaloylchloride for 1 hour and stirred at 25°C for 1 hour. This acylating reagent was dropwise added to the solution for 10 minutes and the solution was then stirred for 1 hour. After the reaction was completed, the solvent was removed and the residue was mixed with 50 ml of ethyl acetate. The resulting solid was filtered and suspended in 10 ml of dichloromethane. The suspension was reacted with 1.0 ml of trifluoracetic acid and 0.5 ml of anisol at 25°C for 1 hour. 20 ml of isopropyl ether was added to the reaction mixture and the resulting solid was filtered. After the unpurified solid was dissolved in an aqueous 50% ethanol, the pH of the solution was adjusted to 1.5 with 4N sulfuric acid and the resulting solution was concentrated under reduced pressure. The residue was chromatographed on silica gel by using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure and lyophilized to obtain 50 mg of the title compound as sulfate salt.

NMR(400MHz,DMSO-d6):

9.14(2H,d,J=7.0Hz), 8.40(2H,d,J=6.3Hz), 8.20~8.40(2H,m), 7.94(1H,t), 7.73~7.77(1H,dd), 7.59~7.62(1H,dd), 5.80~5.84(1H,dd), 5.43~5.65(2H,ABq, J=14.5Hz), 5.56(1H,s), 5.20(1H,d),4.82(1H,m), 4.22(1H,t), 3.90(2H,s), 3.83~3.85(2H,m), 3.34~3.68(2H, Abq, J=18.2Hz), 3.44~3.47(2H,m), 1.84(3H,s)

Example 3

Preparation of 7β-[2-hydroxy-2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



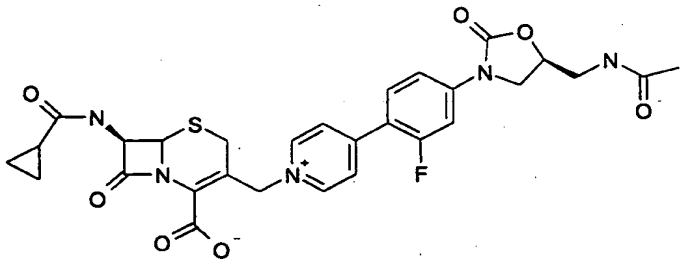
1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 20 ml of dichloromethane and 3 ml of methanol and the resulting soltion was cooled to 5°C. The cold solution was mixed with 0.74 ml of triethylamine and the solution was stirred for 10 minutes. 1.07 g of 2-(4-methoxybenzyloxy)propanoic acid in the Reference Example 3 was added to 10 ml of dichloromethane and the solution was cooled to -30°C. The cold solution was reacted with 0.62 ml of pivaloylchloride for 1 hour and was stirred at 25°C for 1 hour. This acylating reagent was dropwise added and the solution was stirred for 1 hour. 70 mg of the title compound was obtained by the same method in the Example 2.

NMR(400MHz,DMSO-d6):

9.01~9.06(2H,d), 8.42~8.45(2H,d), 8.20~8.40(2H,t), 7.95~8.00(1H,t), 7.73~7.77(1H,dd), 7.60~7.62(1H,dd), 5.75~5.80(1H,dd), 5.45~5.64(2H,ABq), 5.20(1H,d), 4.82(1H,m),4.22(1H,t), 4.07~4.11(1H,m), 3.83~3.85(1H,m), 3.35~3.69(2H, ABq), 3.44~3.47(2H,m), 1.85(3H,s)

Example 4

Preparation of 7β-[2-cyclopropyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



0.1 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 3.0 ml of dimethylformamide and 0.015 ml of cyclopropanecarboxylic acid was added to the solution. Subsequently, 0.03 ml of diethylcyanophosphate was added at 25°C and 0.08 ml of triethylamine was dropwise added for 5 minutes. The solution was stirred at the same temperature for 1 hour. 0.9 ml of isopropyl ether was

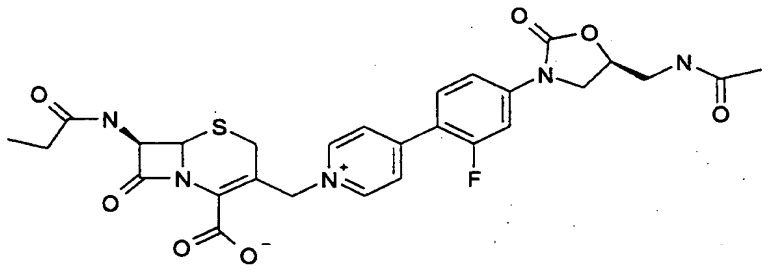
added to the solution and the resulting solid was filtered. The unpurified solid was purified as described in the Example 2 to obtain 10 mg of the title compound as sulfate salt.

NMR(400MHz,DMSO-d6):

9.06(3H,m), 8.43(2H,d), 8.24(1H,t), 7.96(1H,t), 7.74(1H,dd), 7.62(1H,dd), 5.82(1H,dd), 5.45~5.65(2H,ABq), 5.15(1H,d), 5.27(1H,m), 4.83(1H,m), 3.91(1H,m), 3.84(1H,m), 4.22(1H,t), 3.48~3.57(2H, Abq,J=18.2Hz), 3.45(2H,m), 1.93(3H,s), 1.75(1H,m), 0.73(4H,m)

Example 5

Preparation of 7β-[2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



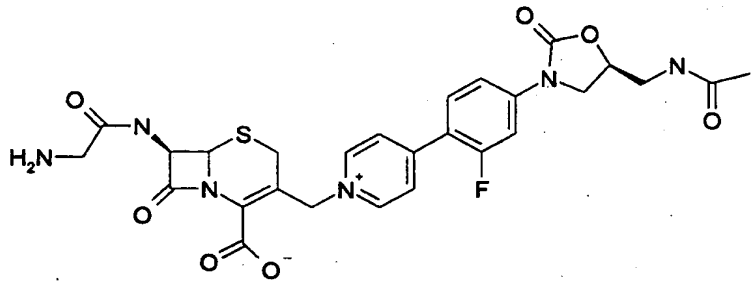
0.5 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 15 ml of dichloromethane and 2.5 ml of methanol and the solution was cooled to 5°C. 0.37 ml of triethylamine was added and the solution was stirred for 10 minutes. 0.6 g of propionic acid was dissolved in 20 ml of dichloromethane and the solution was cooled to -30°C. The cold solution was reacted with 1.23 ml of triethylamine and 0.99 ml of pivaloylchloride for 1 hour and stirred at 25°C for 1 hour. This acylating reagent was dropwise added and the solution was stirred for 1 hour. After the reaction was completed, the solvent was removed and the residue was dissolved in 50% ethanol. The solution was purified as described in Example 2 to obtain 50 mg of the title compound as sulfate salt.

NMR(400MHz,DMSO-d6): 8.98(2H,d), 8.72(1H,d), 8.37(2H,d), 8.20(1H,t),

7.91(1H,t), 7.69(1H,dd), 7.54(1H,dd), 5.75(1H,dd), 5.50(2H,ABq), 5.19(1H,d), 4.76(1H,m), 4.15(1H,t), 3.78(1H,dd), 3.48~3.57(2H,ABq,J=18.1Hz), 3.42(2H,m), 2.10(2H,q), 1.77(3H,s), 0.95(3H,t)

Example 6

Preparation of 7β-[2-amino-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate

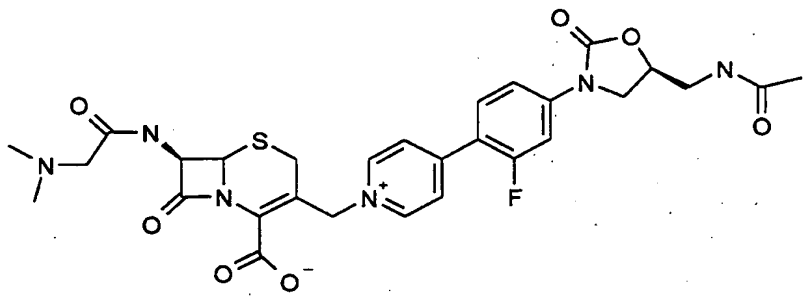


0.3 g of dihydrochloride salt of the title compound in the Reference Example 1 was used as a starting material and 0.12 g of aminoacetylchloride hydrochloride was used as an acylating reagent. 30 mg of the title compound as hydrochloride salt was obtained by the same procedure in Example 1.

NMR(400MHz,DMSO-d6): 9.47(2H,d), 8.66(1H,d), 8.37(2H,d), 8.26(1H,t), 7.95(1H,t), 7.73~7.77(1H,dd), 7.59~7.62(1H,dd), 5.60~5.70(1H,dd), 5.05~5.20(2H,q), 5.56(1H,s), 4.91(1H,d), 4.82(1H,m), 4.22(1H,t), 3.90(2H,s), 3.80~3.85(3H,m), 3.34~3.68(2H, ABq,J=18.2Hz), 3.44~3.47(2H,m), 1.84(3H,s)

Example 7

Preparation of 7β-[2-(N,N'-dimethylamino]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



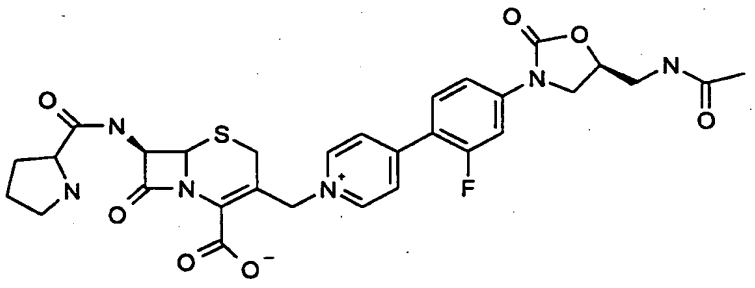
0.3 g of dihydrochloride salt of the title compound in the Reference Example 1 was used as a starting material and 0.18 g of N,N'-dimethylaminochloride hydrochloride was used as an acylating reagent. 20 mg of the title compound as hydrochloride salt was obtained by the same procedure in Example 1.

NMR(400MHz,DMSO-d6):

9.47(2H,d), 8.66(1H,d), 8.37(2H,d), 8.26(1H,t), 7.95(1H,t), 7.73~7.77(1H,dd), 7.58~7.60(1H,dd), 5.90(1H,dd), 5.61~5.66(2H,m), 5.08~5.1(2H,m), 4.83(1H,m), 4.22(1H,t), 4.00~4.10(2H,q), 3.83(1H,dd), 3.40~3.75(2H,ABq), 3.08(6H,s),1.84(3H,s)

Example 8

Preparation of 7β-[perhydro-2-pyrolyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



0.5 g of N-(tert-butoxycarbonyl)-L-pyroline was dissolved in 5.0 ml of tetrahydrofuran. The solution was reacted with 0.38 g of 1-hydroxybenzotriazol and 0.51 g of 1,3-dicyclohexylcarbodiimide at 25°C for 1 hour. The resulting solid was filtered and

the parent liquid was concentrated to obtain an acylating ester reagent.

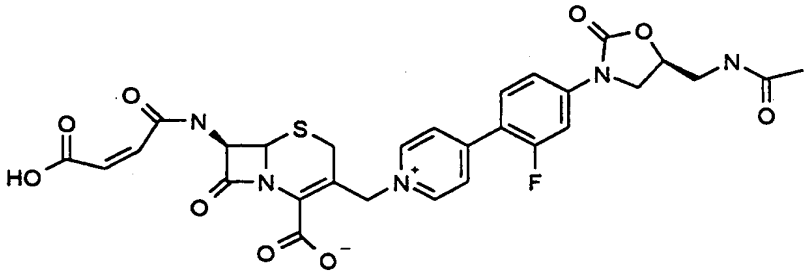
0.2 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 5.0 ml of dimethylformamide and the solution was cooled to 5°C. The 0.1 ml of triethylamine was added and the solution was stirred for 10 minutes. The above prepared acylating reagent in 3.0 ml of dimethylformamide was dropwise added for 10 minutes. Then, the solution was stirred for 1 hour. After the reaction was completed, 10.0 ml of isopropylether was added to the solution and the resulting solid was filtered. The solid was suspended in 5.0 ml of dichloromethane and the suspension was reacted with 1.0 ml of trifluoroacetic acid at 25°C for 1 hour. After the reaction was completed, the solution was concentrated under reduced pressure. 10.0 ml of isopropylether was added and the resulting solid was filtered. The solid was dissolved in 50% ethanol and the solution was concentrated under reduced pressure. The residue was chromatographed over silica gel using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure, and lyophilized to obtain 50 mg of the title compound as trifluoroacetate salt.

NMR(400MHz,DMSO-d6):

9.52(1H,d), 9.03(2H,d), 8.44(2H,d), 8.27(1H,t), 7.97(1H,t), 7.76(1H,dd), 7.62(1H,dd), 5.90(1H,dd), 5.45~5.63(2H,ABq), 5.25(1H,d), 4.84(1H,m), 4.22(2H,m), 3.84(1H,m), 3.63(1H,m), 3.40~3.60(2H,q), 3.20(2H,br), 2.52(1H,m), 1.94(2H,m), 1.85(3H,s), 1.20(2H,m)

Example 9

Preparation of 7β-[2-carboxy-(Z)-1-ethenyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



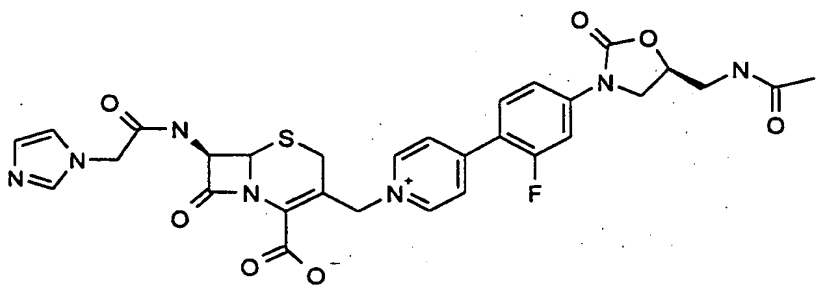
1.0 g of dihydrochloride of Reference Example 1 was used as a starting material and 0.1 g of maleic anhydride was used as an acylating reagent. 10 mg of the title compound as hydrochloride salt was obtained by the same procedure in Example 1.

NMR(400MHz,DMSO-d6):

9.85(1H,br), 9.40~9.43(1H,d,J=6.3Hz), 8.37~8.40(2H,d,J=6.3Hz), 8.28(1H,m), 7.92~7.98(1H,m), 7.72~7.76(1H,m), 7.57~7.60(1H,m), 6.28~6.32(1H,d,J=12.3Hz), 6.17~6.21(1H,d,J=12.3Hz), 5.65~5.68(2H,m), 5.07~5.20(2H,m), 4.80(1H,m), 4.22(2H,m), 4.21(1H,m), 3.84(1H,m), 3.10~3.60(1H,ABq), 3.54(2H,m), 1.85(3H,s)

Example 10

Preparation of 7β-[((1H)-1-imidazolyl)-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



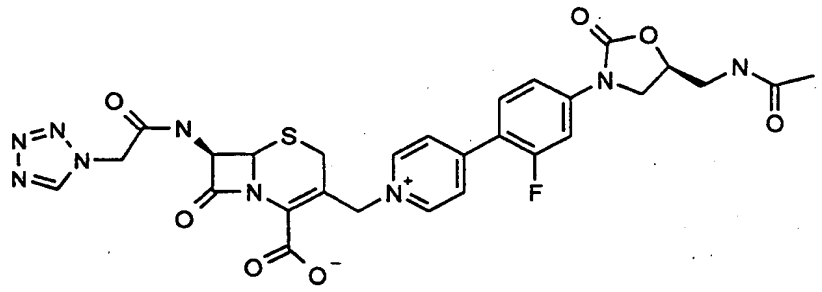
1.0 g of dihydrochloride salt of the title compound in the Reference Example 1 was used as a starting material and 0.22 g of 1H-1-imidazolylacetic acid hydrochloride of the title compound in the Reference Example 4 was used as an acylating reagent. 5 mg of the title compound as sulfate salt was obtained.

NMR(400MHz,DMSO-d6):

9.45(1H,d), 9.20(1H,d), 8.38(2H,m), 8.25(1H,t), 7.95(1H,dd), 7.73(1H,dd), 7.58(2H,m),7.08(1H,s), 6.88(1H,s), 5.66(2H,m), 5.15(1H,d), 5.05(1H,m), 4.73~4.84(3H,m), 4.21(1H,t), 3.83(1H,dd), 3.44(2H,m), 1.84(3H,s)

Example 11

Preparation of 7β-[((1H)-1-tetrazolyl)-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



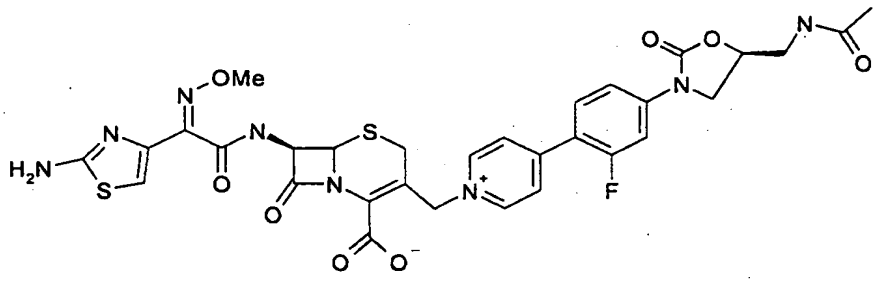
0.5 g of dihydrochloride salt of the title compound in the Reference Example 1 was dissolved in 15 ml of dichloromethane and 2.5 ml of methanol and the solution was cooled to 5°C. The cold solution was mixed with 0.37 ml of triethylamine and the mixture was stirred for 10 minutes. 0.2 g of tetrazoleacetic acid was dissolved in 5 ml of dichloromethane and the solution was cooled to -30°C. The cold solution was reacted with 0.22 ml of triethylamine and 0.2 ml of pivaloylchloride for 1 hour and was stirred at 25°C for 1 hour. This acylating reagent was dropwise added for 10 minutes and the solution was stirred for 1 hour. After the reaction was completed, the solvent was concentrated. The residue was dissolved in 50% ethanol and was purified as described in the Example 1 to obtain 30 mg of the title compound.

NMR(400MHz,DMSO-d6):

9.30~9.47(3H,m), 9.37(1H,s), 8.38(2H,d), 8.27(1H,t), 7.95(1H,t), 7.77(1H,dd), 7.58(2H,dd), 5.16~5.67(2H,ABq,J=13.7Hz), 5.62(1H,dd), 5.30~5.38(2H,ABq,J=16.8Hz), 5.05(1H,d), 4.85(1H,m), 4.22(3H,m), 3.83(1H,t), 3.44(2H,m), 3.15~3.57(2H,ABq,J=17.1Hz), 1.84(3H,s)

Example 12

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



500 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. 0.8 ml of N-methyl-N-(trimethylsylyl)trifluoro acetamid (MSTFA) was added and the solution was stirred for 1.5 hour. After the silylation was completed, the solution was cooled to 5°C and was reacted with 0.5 ml of iodotrimethylsilane at 20°C for 30 minutes. The solution was concentrated under reduced pressure and the residue was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran at 5°C for 5 minutes. The prepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[3-fluor-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the known method (WO 93/19103). 400 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce a silylated pyridine derivative. The formed solid by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered. After the solid was dissolved in an aqueous 30% ethanol, the pH of the resulting solution was adjusted to 6.5 with saturated sodium bicarbonate and was concentrated under reduced pressure. The residue was chromatographed over silica gel using a mixed solvent of acetonitrile and water (4:1), concentrated under reduced pressure, and lyophilized to obtain 100 mg of the title compound.

mp: 178°C to 183°C (decomposition).

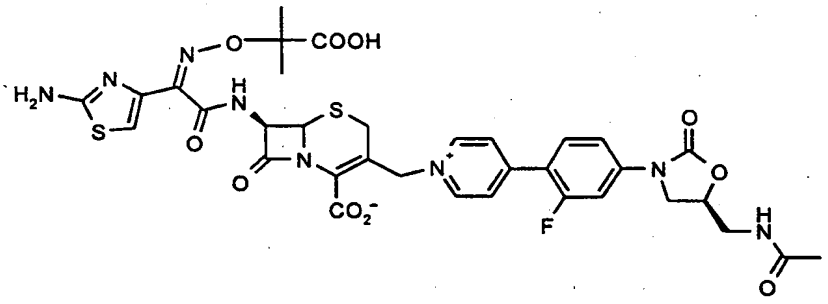
IR(cm^{-1}): 3411, 1760, 1617,

NMR(400MHz,DMSO-d6):

9.60(1H,d,J=8.2Hz), 9.07~9.09(2H,m), 8.40~8.41(2H,m), 8.26~8.28(1H,m), 7.93~7.98(1H,m), 7.57~7.76(2H,m), 7.18(2H,s), 6.72(1H,s), 5.87~5.89(1H,dd), 5.36~5.62(1H,ABq), 5.18~5.20(1H,d), 4.74~4.83(1H,m), 4.22~4.25(1H,m), 3.82~3.87(1H,m), 3.80(3H,s), 3.40~3.50(2H,m), 3.36~3.62(2H,ABq), 1.84(3H,s)

Example 13

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-ethoxyimino) acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



530 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as the Example 12 was carried out by using 1.3 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by silylating 400 mg of (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolydinyl]-methyl]acetamide with MSTFA in 10 ml of acetonitrile. The solution was deprotected by adding 1 ml of methanol, filtered and purified to obtain 120 mg of the title compound.

mp: 174°C to 177°C (decomposition)

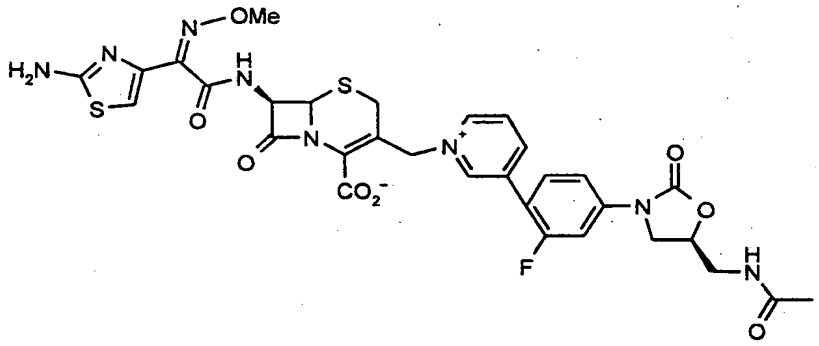
IR(cm-1): 3433, 1760, 1617, 1467, 1151

NMR(DMSO-d6):

9.42~9.45(1H,d,J=8.3Hz), 9.03~9.04(2H,m), 8.42~8.43(2H,m), 8.23~8.24(1H,m), 7.94~7.96(1H,m), 7.59~7.77(2H,m), 7.25(2H,s), 6.70(1H,s), 5.95~5.96(1H,dd), 5.45~5.63(2H,ABq), 5.23~5.24(1H,d), 4.78~4.82(1H,m), 4.22~4.26(1H,m), 3.82~3.88(1H,m), 3.40~3.52(2H,m), 3.30~3.62(2H,q), 1.83(3H,s), 1.41~1.43(6H,d)

Example 14

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridinio methyl]-3-cephem-4-carboxylate



500 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 0.8 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The preprepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the known method (WO 93/09103). 400 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce the silylated pyridine

derivative. The formed solid by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered, and purified to obtain 130 mg of the title compound.

mp: 183°C to 186°C (decomposition)

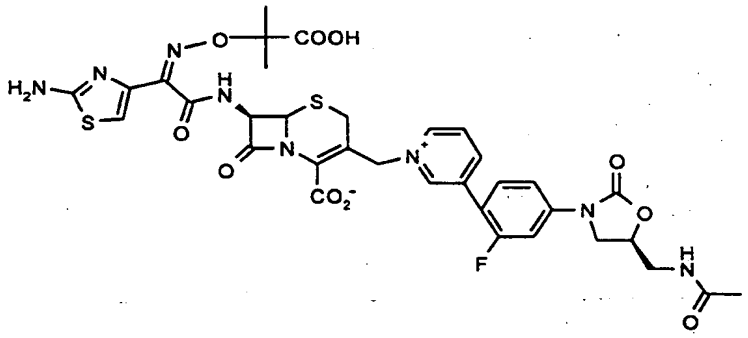
IR(cm-1): 3416, 1760, 1627, 1540, 1040

NMR(DMSO-d6):

9.60(1H,d,J=8.0Hz), 9.37(1H,s), 9.01~9.04(1H,m), 8.86~8.89(1H,m), 8.25~8.31(2H,m), 7.73~~7.84(2H,m), 7.56~7.58(1H,m), 7.19(2H,s), 6.71(1H,s), 5.91~5.94(1H,dd), 5.20~5.21(1H,d), 5.62~5.70(2H,ABq), 4.77~4.82(1H,m), 4.18~4.22(1H,m), 3.81~3.83(1H,m), 3.80(3H,s), 3.40~3.53(2H,m), 3.30~3.63(2H,q), 1.84(3H,s)

Example 15

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino) acetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridinio methyl]-3-cephem-4-carboxylate



530 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 1.3 ml of MSTFA and 0.5 ml of TMSI, the reaction solution was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by silylating 400 mg of (S)-N-[[3-[3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolydinyl]-methyl]acetamide with

MSTFA in 10 ml of acetonitrile. The solution was deprotected by adding 1 ml of methanol, filtered and purified to obtain 100 mg of the title compound.

mp: 175°C to 177°C (decomposition)

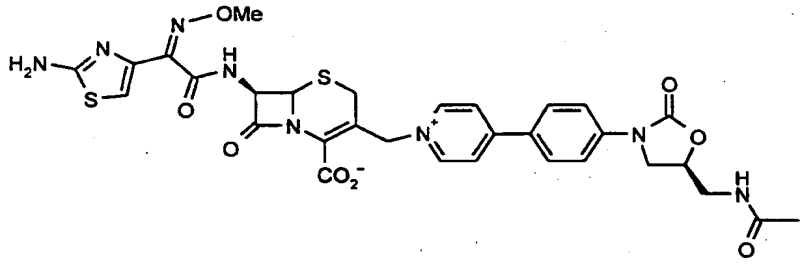
IR(cm^{-1}): 3433, 1760, 1617, 1467, 1151

NMR(DMSO-d6):

9.40~9.44(2H,m), 9.06~9.08(1H,m), 8.84~8.86(1H,m), 8.25~8.30(2H,m), 7.72~7.83(2H,m), 7.55~7.57(1H,m), 7.2(2H,s), 6.69(1H,s), 5.94~5.98(1H,dd), 5.20~5.22(1H,d), 5.60~5.66(2H,ABq), 4.78~4.83(1H,m), 4.16~4.20(1H,m), 3.81~4.84(1H,m), 3.4.~3.51(2H,m), 1.84(3H,s), 1.37~1.40(6H,d)

Example 16

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-mthoxyiminoacetamido]-3-[4-[4-[5-[(S)-methyl-carboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



500 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as the Example 12 was carried out by using 0.8 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The preprepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivative was prepared as follows. (S)-N-[[3-[4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was synthesized according to the known method (USP 5,254,577). 380 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution

was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce the silylated pyridine derivative. The silylated pyridine derivative was added and the solution was stirred at 25°C for 3 hours. The formed solid was filtered by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution, and purified to obtain 150 mg of the title compound. mp: 196°C to 198°C (decomposition)

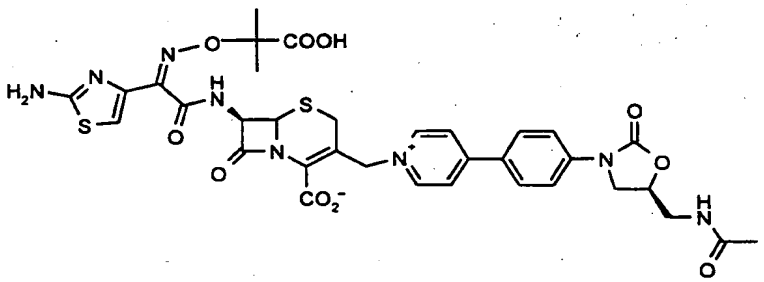
IR(cm^{-1}): 3415, 1791, 1750, 1617,

NMR(DMSO-d6):

9.60(1H,d,J=7.9Hz), 8.78~8.96(2H,d), 8.54~8.56(2H,d), 8.24~8.26(1H,m), 8.16~8.19(2H,m), 7.80~7.82(2H,m), 7.25(2H,s), 6.73(1H,s), 5.87~5.89(1H,dd), 5.22(1H,d), 5.41~5.57(2H,ABq), 4.77~4.84(1H,m), 4.23~4.26(1H,m), 3.82~3.85(1H,m), 3.81(3H,s), 3.40~3.50(2H,m), 3.35~3.65(2H,q), 1.83(3H,s)

Example 17

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino) acetamido]-3-[4-[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



530 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 1.3 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by silylating 380 mg of (S)-N-[[3-[4-(4-pyridyl)phenyl]-2-oxo-5-oxazolydinyl]-methyl]acetamide with MSTFA

in 10 ml of acetonitrile. The solution was deprotected by adding 1 ml of methanol, filtered and purified to obtain 120 mg of the title compound.

mp: 175°C to 177°C (decomposition)

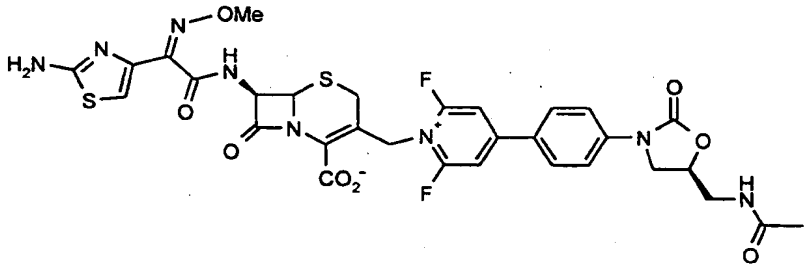
IR(cm-1): 3433, 1760, 1617, 1467, 1151

NMR(DMSO-d6):

9.43~9.46(1H,d), 8.98~9.00(2H,d), 8.54~8.56(2H,d), 8.24~8.27(1H,m), 8.16~8.18(2H,d), 7.89~7.91(2H,d), 7.28(2H,s), 6.70(1H,s), 5.90~5.95(1H,dd), 5.22~5.23(1H,d), 5.45~5.61(2H,ABq), 4.76~4.82(1H,m), 4.18~4.24(1H,m), 3.79~3.84(1H,m), 3.40~3.49(2H,m), 3.30~3.64(2H,q), 1.83(3H,s), 1.38~1.40(6H,d)

Example 18

Preparation of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2,6-difluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



500 mg of 7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. After the same procedure as Example 12 was carried out by using 0.8 ml of MSTFA and 0.5 ml of TMSI, the reaction mixture was concentrated under reduced pressure. The concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The preprepared silylated pyridine derivative was added to the solution at 5°C and the solution was stirred at 25°C for 3 hours. This silylated pyridine derivate was prepared as follows. (S)-N-[[3-[3,5-difluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide was used as a pyridine derivative and was

synthesized according to the known method (WO 93/09103). 420 mg of the pyridine derivative was added to 10 ml of acetonitrile and the resulting solution was reacted with 1.0 ml of MSTFA at 25°C for 2 hours to produce the silylated pyridine derivative. The formed solid by adding 1.0 ml of methanol and 5 ml of acetonitrile to the solution was filtered, and purified to obtain 10 mg of the title compound.

mp: 175°C to 177°C (decomposition)

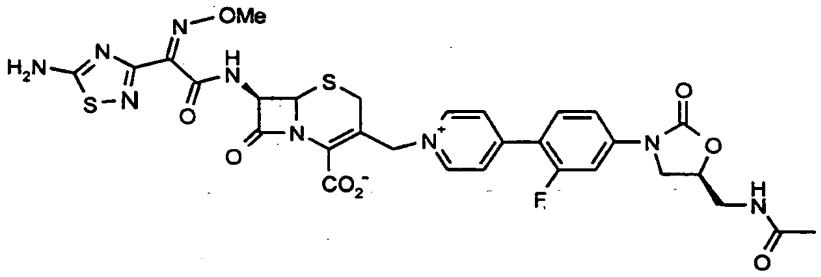
IR(cm^{-1}): 3412, 1760, 1615,

NMR(DMSO-d6):

9.60(1H,d), 9.08~9.10(2H,d), 8.37~8.39(2H,d), 8.23~8.37(1H,m), 7.58~7.61(1H,d), 7.50~7.53(1H,d), 6.74(1H,s), 5.87~5.89(1H,dd), 5.52~5.64(1H,ABq), 5.18~5.21(1H,d), 4.82~4.97(1H,m), 4.21~4.26(1H,m), 3.82~3.87(1H,m), 3.80(3H,s), 3.41~3.51(2H,m), 3.30~3.62(2H,q), 1.85(3H,s)

Example 19

Preparation of 7β-[(Z)-2-(5-amino-1,2,4-thiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate.



500 mg of 7β-[(Z)-2-(5-amino-1,2,4-thiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid [THE JOURNAL OF ANTIBIOTICS: Vol.XXXVI, No.8 p1020-1033(1983), Vol.XXXVII, No.5 p557-571(1984)] was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. 0.8 ml of MSTFA was added and the solution was stirred for 1.5 hour. After the silylation was completed, the solution was cooled to 5°C and was reacted with 0.5 ml of TMSI at 20°C for 30 minutes.

The solution was concentrated under reduced pressure and the residue was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran at 5°C for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by reacting 400 mg of (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolydinyl]-methyl]acetamide with 1.0 ml of MSTFA in 10 ml of acetonitrile. The formed solid by adding a mixed solvent of 1.0 ml of methanol and 5 ml of acetonirile to the solution was filtered. The solid was dissolved in an aqueous 30% ethanol and the pH of the solution was adjusted to 7.0 with saturated sodium bicarbonate. The pH of the solution was then adjusted to 2.0 with 4N sulfuric acid and ethanol was added to the solution to obtain 100 mg of the title compound as sulfate salt.

mp: 165°C or more (decomposition)

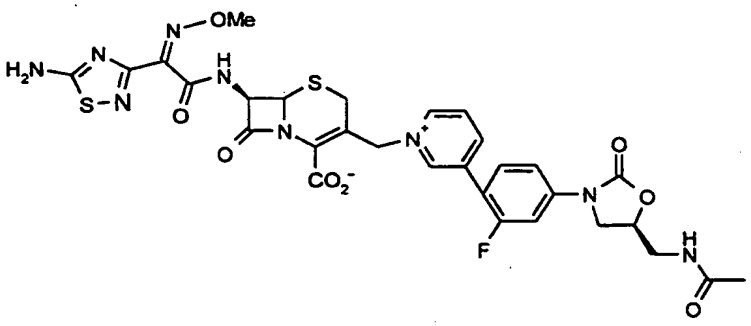
IR(cm-1): 3416, 1757

NMR(DMSO-d6):

9.58(1H,d,J=8.3Hz), 9.10(2H,d), 8.44(2H,d), 8.26(1H,m), 7.94~7.97(1H,m), 7.74~7.77(2H,m), 7.59~7.61(1H,m), 5.82~5.90(1H,dd), 5.18~5.20(1H,d,J=4.9Hz), 5.44~5.62(2H,ABq,J=4.5Hz), 4.74~4.83(1H,m), 4.22~4.25(1H,m), 3.80~3.87(1H,m), 3.88(3H,s), 3.40~3.50(2H,m), 2.9~3.6(2H,m), 1.84(3H,s)

Example 20

Preparation of 7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



500 mg of 7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. The solution was reacted with 0.8 ml of MSTFA and 0.5 ml of TMSI by the same method as the Example 19. The solution was concentrated under reduced pressure and the concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by reacting 400 mg of (S)-N-[[3-[3-fluoro-4-(3-pyridyl)phenyl]-2-oxo-5-oxazolydinyl]-methyl]acetamide with 1.0 ml of MSTFA in 10 ml of acetonitrile. The resulting solid by adding a mixed solvent of 1.0 ml of methanol and 5 ml of acetoniril to the solution was filtered. The solid was dissolved in an aqueous 30% ethanol and the pH of the solution was adjusted to 7.0 with saturated sodium bicarbonate. The pH of the solution was then adjusted to 2.0 with 4N sulfuric acid and ethanol was added to the solution to obtain 110 mg of the title compound as sulfate salt.

mp: 145°C or more (decomposition)

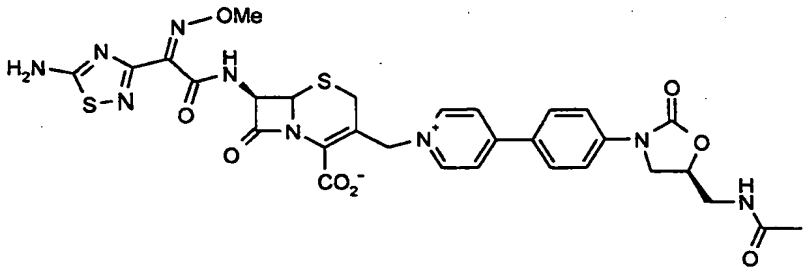
IR(cm-1): 3418, 1760

NMR(DMSO-d6):

9.50~9.56(2H,m), 9.20(1H,s), 8.80~8.85(1H,m), 8.25~8.32(2H,m), 7.70~7.85(2H,m), 7.50~7.60(1H,m), 5.82~5.89(1H,dd), 5.20(1H,d), 5.50~5.70(2H,ABq), 4.76~4.82(1H,m), 4.18~4.23(1H,m), 3.80~3.85(1H,m), 3.86(3H,s), 3.40~3.50(2H,m), 1.85(3H,s)

Example 21

Preparation of 7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate



500 mg of 7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-acetoxymethyl-3-cephem-4-carboxylic acid was dissolved in 10 ml of anhydrous dichloromethane under nitrogen. The solution was reacted with 0.8 ml of MSTFA and 0.5 ml of TMSI by the same method as the Example 19. The solution was concentrated under reduced pressure and the concentrate was reacted with 10 ml of acetonitrile and 1 ml of tetrahydrofuran for 5 minutes. The solution was reacted at 25°C for 3 hours with the silylated pyridine derivatives obtained by reacting 380 mg of (S)-N-[[3-[4-(4-pyridyl)phenyl]-2-oxo-5-oxazolydinyl]-methyl]acetamide with 1.0 ml of MSTFA in 10 ml of acetonitrile. The resulting solid by adding a mixed solvent of 1.0 ml of methanol and 5 ml of acetonirile to the solution was filtered. The solid was dissolved in an aqueous 30% ethanol and the pH of the solution was adjusted to 7.0 with saturated sodium bicarbonate. The pH of the solution was then adjusted to 2.0 with 4N sulfuric acid and ethanol was added to the solution to obtain 150 mg of the title compound as sulfate salt.

mp: 170°C or more (decomposition)

IR(cm-1): 3415, 1760

NMR(DMSO-d6):

9.58(1H,d), 8.80~9.00(2H,d), 8.54~8.58(2H,d), 8.24~8.26(1H,m), 8.16~8.20(2H,m), 7.80~7.84(2H,m), 5.85~5.90(1H,dd), 5.18~5.20(1H,d), 5.42~5.60(2H,ABq), 4.78~4.83(1H,m), 4.22~4.25(1H,m), 3.80~3.85(1H,m), 3.87(3H,s), 3.40~3.50(2H,m), 1.84(3H,s)

Antibacterial Activity Test

The *in vitro* antibacterial activities of the compounds prepared by Examples 1 through 21 were tested as described in Chemotheraphy, 29(1), 76, 1981. Vancomycin and cefotaxime were used as control. Their MICs (Minimum Inhibition Concentration: μg/ml) by agar dilution were measured and the result is indicated in Table 2 below.

Table 2

	A	B	C	D	E	F	G	H	I
1	0.50	1.00	1.00	0.25	1.00	0.06	32.0	4.00	>32.0
2	1.00	1.00	1.00	0.25	0.50	0.06	32.0	2.00	>32.0
3	1.00	1.00	1.00	0.25	1.00	0.06	>32.0	2.00	>32.0
4	1.00	2.00	2.00	0.50	2.00	0.06	32.0	4.00	>32.0
5	1.00	2.00	2.00	0.50	2.00	0.06	>32.0	8.00	>32.0
6	2.00	1.00	1.00	0.50	1.00	0.25	>32.0	8.00	>32.0
7	2.00	2.00	2.00	0.50	1.00	0.25	>32.0	4.00	>32.0
8	2.00	2.00	2.00	1.00	2.00	0.50	>32.0	32.0	>32.0
9	8.00	4.00	4.00	2.00	8.00	1.00	>32.0	16.0	>32.0
10	1.00	1.00	1.00	0.25	1.00	0.06	>32.0	4.00	>32.0
11	1.00	2.00	2.00	0.25	4.00	0.06	8.00	4.00	>32.0
12	1.00	2.00	1.00	0.25	1.00	0.06	0.12	0.06	1.00
13	2.00	2.00	2.00	1.00	2.00	0.12	0.25	0.12	0.50
14	2.00	2.00	2.00	0.50	2.00	0.06	0.25	0.25	2.00
15	2.00	2.00	2.00	0.50	2.00	0.06	0.12	0.25	1.00
16	2.00	4.00	4.00	0.50	2.00	0.06	0.25	0.12	0.25
17	2.00	4.00	4.00	1.00	2.00	0.12	0.50	0.25	1.00
18	2.00	2.00	2.00	0.50	2.00	0.50	2.00	0.25	0.50
19	1.00	2.00	2.00	1.00	2.00	0.06	0.12	0.06	2.00
20	2.00	2.00	2.00	0.50	2.00	0.06	0.12	0.25	0.50
21	2.00	4.00	4.00	1.00	4.00	0.06	0.12	0.25	2.00
C1	0.25	0.25	0.25	0.25	0.25	0.06	32	0.25	32
C2	2.00	32	128	1.00	128	0.06	0.06	0.06	0.06
C3	1.00	1.00	1.00	1.00	2.00	0.25	128	128	128

A: *Staphylococcus aureus* ATCC29213

B: MRSA C5100 (Methicillin resistant *Staphylococcus aureus*)

C: CRSA C6043 (Ciprofloxacin resistant *Staphylococcus aureus*)

D: *Staphylococcus epidermis* ATCC12228

E: *Enterococcus faecalis* ATCC29212

F: *Streptococcus pyogenes* ATCC8668

G: *Escherichia coli* ATCC10536

H: *Klebsiella pneumoniae* ATCC10031

I: *Proteus mirabilis* ATCC25933

C1: (S)-N-[[3-[3-fluoro-4-(4-pyridyl)phenyl]-2-oxo-5-oxazolidinyl]-methyl]acetamide

C2: Cefotaxime

C3: Vancomycin

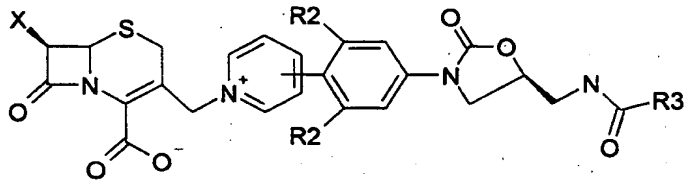
As can be seen from the above Table 2, the compounds of the formula I according to the present invention are broadly active against Gram-positive and Gram-negative bacteria and have the pharmacological advantages of vancomycin and cefotaxime. Especially, the compounds of the formula I are advantageous in that they are effective against cephem antibiotics-registant bacteria such as MRSA and CRSA.

Toxicity Test

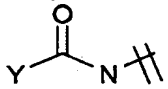
The single dose toxicity of the compounds of the present invention was evaluated in ICR mice by intravenous administration. The compounds of Examples 1, 2 and 13 along with an equivalent of sodium bicarbonate were dissolved in saline and the resulting solutions were intravenously administered. LD_{50} of each test compound was measured to be 1,500 mg/kg of weight.

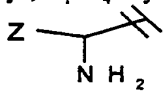
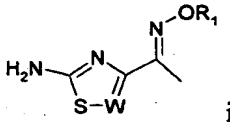
WHAT IS CLAIMED IS:

1. A compound of the formula I:



or pharmaceutically acceptable salts or hydrates thereof wherein

X is i) amine or protected amine, ii)  in which Y is i) hydrogen, ii) C_1-C_6 lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iii) C_2-C_6 alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C_2-C_6 alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4 acyloxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, vi) R4-(CH_2)n-,

in which n is an integer of 0 to 3, and R4 is 2-thiophenyl, 2-furyl, 2-pyrolyl, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 acylamino, C_1-C_4 alkylsulfonylamino, C_1-C_4 alkoxy, and C_1-C_4 acyloxy, vii)  in which Z is hydrogen, or C_1-C_6 lower alkyl, C_1-C_6 alkenyl, C_2-C_6 alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, and carbon having optical activity can be optically pure (-), (+) or racemic forms, viii)  in which W is CH or N, R_1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different;

R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and

provided that in the compounds of the formula I the phenyloxazolidinone is substituted at 3 or 4 positions of pyridine.

2. The compound according to claim 1 in which R2 is independently hydrogen or fluorine.

3. The compound according to claim 1 in which R3 is hydrogen, methyl, difluoromethyl, trichloromethyl, hydroxymethyl or methoxy.

4. The compound according to claim 1 which is

7β-acetamido-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[2-hydroxy-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[2-hydroxy-2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[2-cyclopropyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[2-methyl-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[2-amino-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[2-(N,N'-dimethylamino]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[perhydro-2-pyrolyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[2-carboxy-(Z)-1-ethenyl-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[((1H)-1-imidazolyl)-carboxamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[((1H)-1-tetrazolyl)-acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamido-methyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-ethoxyimino)acetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-[5-[(S)-

methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[(Z)-2-(2-aminothiazol-4-yl)-2-(1-carboxy-1-methyl-1-ethoxyimino)acetamido]-3-[4-[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

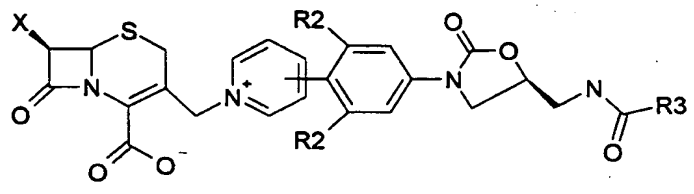
7β-[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamido]-3-[4-[2,6-difluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

7β-[(Z)-2-(5-amino-1,2,4-thiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate;

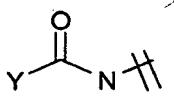
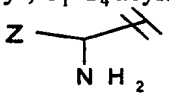
7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[3-[2-fluoro-4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate; or

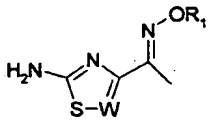
7β-[(Z)-2-(5-amino-1,2,4-thiadiazol-3-yl)-2-methoxyiminoacetamido]-3-[4-[4-[5-[(S)-methylcarboxamidomethyl]-2-oxo-1,3-oxazol-3-yl]phenyl]-1-pyridiniomethyl]-3-cephem-4-carboxylate.

5. A process for producing a compound of the formula I:



or pharmaceutically acceptable salts or hydrates thereof wherein

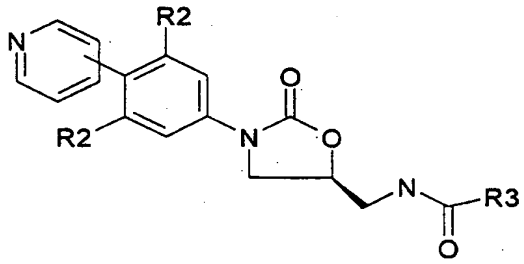
X is i) amine or protected amine, ii)  in which Y is i) hydrogen, ii) C_1-C_6 lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iii) C_2-C_6 alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C_2-C_6 alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4 acyloxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, vi) R4-(CH_2)n-, in which n is an integer of 0 to 3, and R4 is 2-thiophenyl, 2-furyl, 2-pyrolyl, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 acylamino, C_1-C_4 alkylsulfonylamino, C_1-C_4 alkoxy, and C_1-C_4 acyloxy, vii)  in which Z is hydrogen, or C_1-C_6 lower alkyl, C_1-C_6 alkenyl, C_2-C_6 alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of

chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, and carbon having optical activity can be optically pure (-), (+) or racemic forms, viii)  in which W is CH or N, R_1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

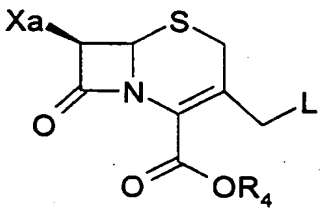
R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different;

R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and

provided that in the compounds of the formula I the phenyloxazolidinone is substituted at 3 or 4 positions of pyridine, which comprises reacting a compound of the formula II:

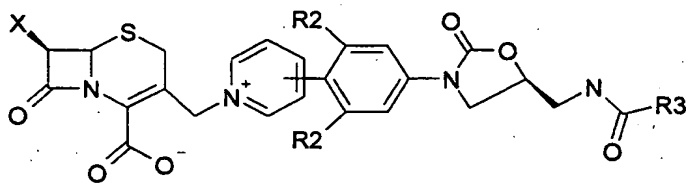


wherein R2 and R3 are same as defined above, with a compound of the formula III:

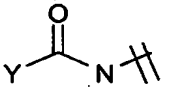


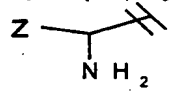
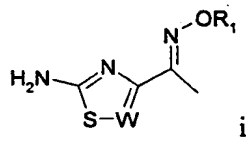
wherein Xa is the same as X defined above, except for amine and protected amine, R_4 is hydrogen or carboxylic acid-protecting group, and L is halogen atom or acetoxy, to produce the compound of the formula I.

6. A process for producing a compound of the formula I:



or pharmaceutically acceptable salts or hydrates thereof wherein

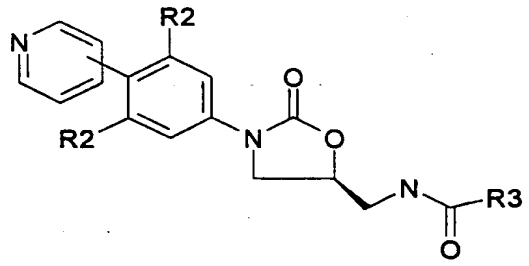
X is i) amine or protected amine, ii)  in which Y is i) hydrogen, ii) C_1-C_6 lower alkyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iii) C_2-C_6 alkenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, iv) C_2-C_6 alkynyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, v) phenyl optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4 acyloxy, C_1-C_4 alkylsulfonyl, C_1-C_4 alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, vi) R4-(CH_2)n-, in which n is an integer of 0 to 3, and R4 is 2-thiophenyl, 2-furyl, 2-pyrolyl, 4-thiazolyl, 1,2,4-thiadiazol-3-yl, 2-oxazolyl, or 5- or 6- membered heterocyclic compound having

from 1 to 4 atoms of O, S and N which are substituted with at least one selected from the group consisting of chlorine, fluorine, hydroxy, amino, C_1-C_4 alkyl, C_1-C_4 acylamino, C_1-C_4 alkylsulfonylamino, C_1-C_4 alkoxy, and C_1-C_4 acyloxy, vii)  in which Z is hydrogen, or C_1-C_6 lower alkyl, C_1-C_6 alkenyl, C_2-C_6 alkynyl, phenyl or heterocyclic compound optionally substituted with at least one selected from the group consisting of chlorine, fluorine, cyano, nitro, hydroxy, amino, C_1-C_4 alkylamino, C_1-C_4 dialkylamino, hydroxylamino, C_1-C_4 alkoxyamino, C_1-C_4 alkoxyimino, C_1-C_4 alkoxy, C_1-C_4acyloxy, C_1-C_4alkylsulfonyl, C_1-C_4alkylsulfenyl, C_1-C_4 alkylsulfinyl, C_1-C_4 alkylaminosulfonyl, and carboxylic acid and inorganic cation salt thereof, and carbon having optical activity can be optically pure (-), (+) or racemic forms, viii)  in which W is CH or N, R_1 is hydrogen, or lower alkyl optionally substituted with carboxylic acid or inorganic cation salt thereof or protected carboxylic acid, and the alkoxyimino is a syn isomer;

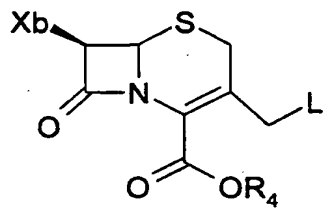
R2 is hydrogen, fluorine, chlorine or methoxy and can be same or different;

R3 is hydrogen, or lower alkyl optionally substituted with carboxy or inorganic cation salt thereof, amino or alkoxy; and

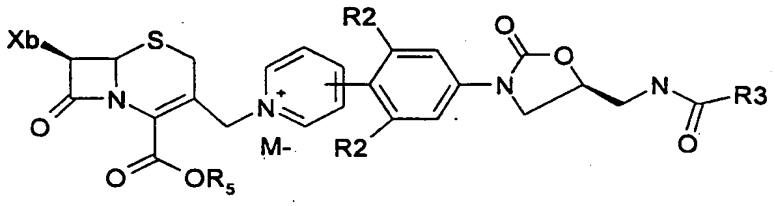
provided that in the compounds of the formula I the phenyloxazolidinone is substituted at 3 or 4 positions of pyridine, which comprises reacting a compound of the formula II:



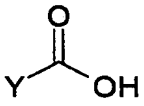
wherein R2 and R3 are same as defined above, with a compound of the formula IV:



wherein Xb is amine or protected amine, R_4 is hydrogen or carboxylic acid-protecting group, and L is the same as defined above, to produce a compound of the formula V:



wherein R2 and R3 are the same as defined above, Xb is amine or protected amine, R_5 is hydrogen or carboxylic acid-protecting group, M^- is anionic halogen, or sulfate, acetate, benzenesulfonate or citrate anions, with the compounds of the formula VI:



wherein Y is the same as defined above, to produce the compound of the formula.

7. An antibacterial composition comprising antibacterially effective amount of the compound according to claim 1 and pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00463

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 501/24; A 61 K 31/545

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 501/24

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 93/09 103 A1 (THE UPJOHN COMPANY) 13 May 1993 (13.05.93), claim 1 (cited in the application).	1-7
A	US 5 254 577 A (CARLSON et al.) 19 October 1993 (19.10.93), claims 1,16,31 (cited in the application).	1-7

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed

„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 March 1999 (08.03.99)	17 March 1999 (17.03.99)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Brus Telephone No. 1/53424/519

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 98/00463

WO 93/09 103 A1

The present invention discloses novel substituted aryl- and heteroarylphenoxazolidinones which are useful as antibacterial agents. More specifically, the substituted aryl- and heteroarylphenyl oxazolidinones of the invention are characterized by oxazolidinones having an aryl or heteroaryl group at the *p*-position of the 3-phenyl ring and additional substitutions at the *m*-position(s) of the 3-phenyl ring. A compound representative of this new class of oxazolidinones is (±)-5-(acetamidomethyl)-3-[4-(3-pyridyl)-3,5-difluorophenyl]-2-oxazolidinone.

US 5 254 577 A

Novel aminomethyloxooxazolidinyl arylbenzene derivatives, wherein the aryl includes the phenyl, substituted phenyl, pyridyl, and substituted pyridyl groups, such as (1)-N-{3-[4-(4`-pyridyl)= phenyl]-2-oxooxazolidin-5-ylmethyl}-acetamide, possess useful antibacterial activity.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 98/00463

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9309103	13-05-93	AT E 146783	15-01-97
		AU A1 26898/92	07-06-93
		AU B2 667198	14-03-96
		DE D0 69216251	06-02-97
		DE T2 69216251	15-05-97
		DK T3 610265	09-06-97
		EP A1 610265	17-08-94
		EP B1 610265	27-12-96
		GR T3 3022340	30-04-97
		JP T2 7500603	19-01-95
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		US A 5654428	05-08-97
		US A 5654435	05-08-97
		US A 5756732	26-05-98
		US A 5801246	01-09-98
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		CA A1 1337526	07-11-95
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		DK A 3743/89	30-01-90
		EP A2 352781	31-01-90
		EP A3 352781	11-07-90
		FI A0 893618	28-07-89
		FI A 893618	30-01-90
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		NO A 893076	30-01-90
		NZ A 230108	25-10-91
		PT A 91315	08-02-90
		US A 4948801	14-08-90
		ZA A 8905778	27-03-91
		US A 5043443	27-08-91
		US A 5130316	14-07-92